Acrodermatitis Acidemica Associated with Deficiency of Branched Chain Amino Acids in Maple Syrup Urine Disease

-A Case Report and Review of the Literature

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Acrodermatitis acidemica is a form of various enzyme defects involving the metabolism of branched-chain amino acids (BCAAs) along with cutaneous features reminiscent of acrodermatitis enteropathica. We report a case of acrodermatitis acidemica associated with a deficiency of BCAAs in maple syrup urine disease. This 2-month-old 4402-gram in weight Paiwanese boy, an aboriginal Taiwanese, was diagnosed as having maple syrup urine disease by severe diarrhea being the main determining factor. A special milk formula free from BCAAs was used since diagnosis. Two weeks later, he began to suffer from progressive sharply demarcated erythematous erosions with weeping surface over his face, neck, anogenital area, bilateral antecubital fossae and four extremities as well as dry desquamation over the bilateral shoulders. In addition, frequent loose stool passages were noted. Blood examinations revealed that the level of the three essential BCAAs, including leucine, isoleucine, and valine were all below the normal limits. Improvement of the skin rash was observed after adding the above-mentioned essential BCAAs in his ordinary diet for 1 week. (Dermatol Sinica 27: 122-127, 2009)

Key words: Acrodermatitis acidemica, Branched chain amino acids, Maple syrup urine disease

INTRODUCTION

Acrodermatitis acidemica, also known as acrodermatitis enteropathica-like eruption, is a form of various enzyme defects involving the branched-chain amino acid (BCAA) metabolism with cutaneous features reminiscent of acrodermatitis enteropathica. It has been described in patients with branched-chain organic acid disorders (methylmalonic and propionic aciduria, and maple syrup urine disease). Maple syrup urine disease (MSUD) is an autosomal recessive inheri-
tance disorder caused by a deficiency of the branched-chain ketoacid dehydrogenase complex, an enzyme common in the degradative pathway of the three BCAAs: leucine, isoleucine, and valine. The mainstay treatment is a synthetic formula devoid of the three BCAAs mentioned above. However, caution should be addressed to supplement the BCAAs with adequate dosage and at adequate intervals. Otherwise, acrodermatitis acidemica ensues. We herein report a case of a 2-month-old boy of MSUD with the classic...
signs of acrodermatitis acideumica. Administration of oral essential BCAAs to his ordinary diet resulted in complete resolution of the dermatitis within 2 weeks.

CASE REPORT

A 2-month-old boy of Paiwanese descent was born full term with adequate birth weight. He had MSUD diagnosed at birth and received a BCAA-free milk formula (MSUD diet powder, Mead Johnson) as his daily feeding (100cc supplement 5-6 times per day). Leucine, isoleucine, and valine were also added in adequate dosages.

The patient gained weight with time but his family didn’t supplement an adequate dosage of the essential BCAAs mentioned above to his regular nutritional regimen at home. Progressive sharply demarcated erythematous erosions with weeping surface over the face, neck, anogenital area, bilateral antecubital fossae and four extremities (Fig. 1A, 1B, 1C) along with dry scaly desquamation over the bilateral shoulders (Fig. 1D) ensued for 3 days. Superficial oral aphthous-like lesions were also observed. Meanwhile, diarrhea frequenting around 6 times per day occurred at the same time. A biopsy taken from the junction of psoriasiform and eczematous plaques on his right shoulder demonstrated mild hyperkeratosis with irregular acanthosis and mild perivascular mononuclear infiltrate in superficial dermis. Neither hypogranulosis nor keratinocytes ballooning change was noted. No fungal element was found by potassium hydroxide scraping. Abnormal laboratory data included an elevated total white blood count (12700/mm³) with a differential of eosinophils: 1%, and normocytic anemia (hemoglobin 10.4g/dl). In addition, inborn error urine screening, including ferric chloride, 2,4-dinitrophenylhydrazine, cyanide nitroprusside, acid albumin turbidity and Benedict’s test, was unremarkable. The serum albumin was 2.3 g/dl (3.7-5.3). The blood levels of iron, total iron-binding capacity, and zinc were all within the normal ranges. However, a deficiency of the three BCAAs was confirmed with a low serum level of leucine: 83.8 μmol/L (83-180), isoleucine: 24.0 μmol/L (49-108), and valine: 81.7 μmol/L (141-261). Under the impression of acrodermatitis acideumica associated with deficiency of BCAAs, oral supplementation of BCAAs was prescribed to supplement his ordinary dietary regimen.

The skin rash improved within 1 week, and cleared in 2 weeks (Fig. 2). With adequate dietary management, there were no subsequent skin eruptions within the following 6 months.
DISCUSSION

MSUD, a rare metabolic disease that was first described by Menkes et al. in 1954, is an autosomal recessive inborn error disorder resulting from the deficiency in a subunit of the mitochondrial branched-chain ketoacid dehydrogenase complex. This complex catalyzes the oxidative decarboxylation of branched-chain ketoacids derived from the transamination of BCAAs, including leucine, isoleucine, and valine. Accumulations of BCAAs and branched-chain ketoacids seemed to induce ketoacidosis, neurological disorder, and developmental disturbance in patients with MSUD. The incidence of MSUD is 1 in 185,000 births throughout the world. In Taiwan, fewer than 10 MSUD cases without accompanying gene analysis have been reported since 1986. The incidence is found to be much higher in the aboriginal tribes of Taiwan. Chi et al. reported that the E2 gene 4.7kb deletion is not only the first MSUD genetic mutation identified in Taiwan but also a founder mutation in the Paiwan tribe, who are one of the nine groups of the aboriginal tribes of Taiwan.

Acrodermatitis acidemica, a nutrition disease occurring among children, was proposed with a similar cutaneous presentation of acrodermatitis enteropathica owing to various enzyme defects involving the metabolism of BCAAs. It is seen in a variety of conditions including cystic fibrosis, necrotic migratory erythema, anorexia nervosa, maple syrup urine disease, methylmalonic academia, propionic academia, biotinidase deficiency (biotin-responsive multiple carboxylase deficiency), citrullinemia, and essential fatty acid deficiency. Systemic presentations include lethargy, failure to thrive, vomiting, dehydration, dyspnea, and hypotonia. Sharply demarcated ooze erythema with desquamation in the diaper region, the neck folds, the periorificial areas (mouth, nose, ears, eyes, and perineum) and the extremities are typical cutaneous manifestations. At first, a vesiculobullous eruption with erosions occurs, and then progresses to dry, hyperkeratotic, and psoriasiform in appearance. Furthermore, scalp hairs might be sparse, brittle, or hypopigmented. Histopathological findings show pallor of the upper part of the epidermis with necrosis of keratinocytes. A diffuse parakeratosis is seen overlying the pale epidermal cells. Sometimes a subcorneal vesicle is present above the area of paleness of the epidermis. The differential diagnosis of acrodermatitis acidemica includes Kwashiorkor, chronic mucocutaneous candidiasis, Langerhans cell histiocytosis, Stevens-Johnson syndrome/toxic epidermal necrolysis, staphylococcal scaled skin syndrome and multiple carboxylase deficiency. As the skin rash and histopathological changes of acrodermatitis acidemica are quite similar to those of acrodermatitis enteropathica, the diagnosis is based on laboratory surveys and past history.

Sparker et al. first reported eight infants with MSUD and acrodermatitis acidemica. Those patients all had low plasma levels of isoleucine and the severity of the dermatitis was correlated with the duration of the isoleucine abnormality. Giacoia and Berry described the cutaneous manifestations of acrodermatitis acidemica, diarrhea and anemia related to isoleucine deficiency. The deficiency of essential amino acids seems to result in epidermal dysfunction because the growth of keratinocytes is arrested, which is especially evident in isoleucine deficiency. As the deficiency becomes more severe, other tissues with high turnover rate, such as mucous membranes, intestinal mucosa, and bone marrow red blood cell progenitors may all be affected. The clinical symptoms and signs of isoleucine deficiency include body weight loss, erythematous swelling of the oral mucosa, desquamation of the skin, and shivering of the hands. Poor feeding, ir-
ritability, body weight loss and lethargy may occur when a deficiency of leucine or valine exists. There is a marked improvement in diarrhea and edema once the proper amount of BCAAs is supplemented. The main tool of long-term therapy is a synthetic formula devoid of leucine, isoleucine, and valine and adding appropriate amounts of these BCAAs during proper intervals in the patient’s regular diet. The suggested supplementation to the dietary regimen is adding 190 μmol/L leucine per 7-10 days, 105 μmol/L isoleucine per 1-3 days and 300 μmol/L valine per 2-4 days.

In conclusion, it is very significant for dermatologists to recognize the features of acrodermatitis acidemica and be aware of the combination in the history of MSUD or other metabolic diseases so as to treat patients timely and avoid detrimental consequences. Surveying the plasma amino acid profile is necessary when facing patients who are suspicious for acrodermatitis acidemica. Thus, an early diagnosis and subsequent metabolic control are the most important determinants of long-term outcome.

REFERENCES
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於一楓糖尿症患者
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酸血性肢端皮膚炎是一種與支鏈胺基酸代謝酵素缺乏有關的疾病，其皮膚表徵與腸病性肢端皮膚炎相似。我們報告一楓糖尿症患者發生酸血性肢端皮膚炎合併支鏈氨基酸缺乏的病例。一個兩個月大四千四百零二克排灣族男孩因嚴重腹瀉而被診斷出楓糖尿症。該病患因而開始餵食不含支鏈胺基酸的配方奶粉。然而在兩週後，他的臉上、頸部、生殖器肛門處、雙側肘窩及四肢出現漸進性輪廓鮮明紅色糜爛病灶及潮濕表面，而且在雙肩出現乾性皮屑。此外，也出現頻繁性軟便。血液檢查結果顯示三種必需支鏈胺基酸包含白胺酸，異白胺酸，頑胺酸皆低於正常值。在他的平日飲食中添加上述必需支鏈胺基酸，其臨床症狀在一周後逐漸改善。（中華皮誌：27: 122-127, 2009）